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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,606	02/27/2004	Mary E. Brunkow	31173/40002	9642

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EXAMINER	
XIE, XIAOZHEN	
ART UNIT	**PAPER NUMBER**
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/788,606	BRUNKOW ET AL.	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *88,89 and 91-109* is/are pending in the application.

4a) Of the above claim(s) *97-100 and 107-109* is/are withdrawn from consideration.

5)☐ Claim(s) *89* is/are allowed.

6)☒ Claim(s) *88,91-96 and 101-106* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20080602*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

The Information Disclosure Statement (IDS) filed 2 June 2008 has been entered. Applicant's amendment of the claims filed on 27 May 2008 has been entered.

Claims 1-87 and 90 are cancelled. Claims 88, 89, 91-109 are pending. Claims 97-100 and 107-109 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 88, 89, 91-96 and 101-106 are under examination.

Claim Objections Withdrawn

The objection to claim 102 for informalities is withdrawn in response to Applicant's amendment of the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 88, 91-96 and 101-106 remain rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for:

1) an isolated antibody or antigen binding fragment thereof which specifically binds to the polypeptide encoded by a polynucleotide selected from the group consisting of SEQ ID Nos:1, 5, 9, 11, 13, or 15; and

2) an isolated antibody or antigen binding fragment thereof which specifically binds to a polypeptide encoded by a polynucleotide having at least 90% identity to a polynucleotide selected from the group consisting of SEQ ID Nos:1, 5, 9, 11, 13, or 15;

wherein said polypeptide retains a cysteine backbone comprising eight cysteines and retains the ability to decrease one mineral content,

does not reasonably provide enablement for antibodies or antigen binding fragments thereof that bind to variants or fragments of the polypeptides encompassed by the genus which hybridize under the recited hybridization conditions. The basis of this rejection is set forth in the previous office actions and the following.

Applicant argues that the specification provides teaching that guides one of ordinary skill in the art where to make additions, substitutions or deletions, and how to screen the resulting variants for activity (e.g., the ability to decrease bone mineral content), for example, the specification states that the cysteine backbone of the protein should generally be conserved. Applicant argues that the specification provides seven different sequences of native mammalian (human, vervet, mouse, rat and bovine) and variant human cDNA encoding a protein that decreases bone mineral content (SEQ ID NOs: 1, 5, 7, 9, 11, 13 and 15), from which one can determine which amino acids and regions are conserved among mammalian species. Applicant provides a sample alignment showing conserved residues among the coding regions of these mammalian

sequences (Appendix A). Applicant argues that the discussion in the action fails to consider this guidance in the specification, i.e. retention of the cysteine backbone, and knowledge of conserved regions in other mammalian species and human variants, and why it would be undue experimentation to produce such variants that retain the desired activity. Applicant further argues that under the wash conditions recited in claim 88, it would be estimated that about 80% homology is required for successful hybridization. Applicant also argues that claims 101-106 recite SEQ ID NO: 1 or polypeptides encoded by naturally occurring polynucleotides, and it is not undue experimentation to use the known techniques of hybridization screening to screen any one of a number of mammalian or human DNA libraries for polynucleotides that encode orthologs or allelic variants of sclerostin, and a number of exemplary sequences obtainable in such a manner have been provided in the specification (SEQ ID NOS: 1, 5, 7, 9, 11, 13 and 15). Applicant further argues that the specification on pages 38-40 describes how to make antibodies comprising effector or reporter molecules, and the method for linked to antibodies and the use of such reporter or effector molecules to enhance the properties of antibodies was known to those in the art prior to the filing date of the application.

Applicant's argument has been fully considered, but has been found to be partially persuasive.

The claims encompass a large genus of antibodies and antigen-binding fragments thereof that the specification fails to provide sufficient guidance as to its make and use.

The genus encompass: 1) an isolated antibody or antigen-binding fragment thereof which specifically binds to a polypeptide, wherein the polypeptide is encoded by a first polynucleotide capable of binding under conditions as recited in claim 88 to a second polynucleotide selected from the group consisting of fully complementary sequences to any of SEQ ID NOs: 1, 5, 7, 9, 11, 13 and 15; wherein the polypeptide retains a cysteine backbone comprising eight cysteines and retains the ability to decrease bone mineral content; 2) a polypeptide comprising an antibody, or an antibody fragment thereof, wherein the polypeptide binds to a polypeptide encoded by SEQ ID NO: 1 with an affinity $K_a \geq 10^7\ M^{-1}$; and 3) a polypeptide comprising an antibody, or an antibody fragment thereof, wherein the polypeptide binds with an affinity $K_a \geq 10^7\ M^{-1}$ to a polypeptide encoded by a naturally occurring polynucleotide that (i) encodes a protein that decreases bone mineral content, and (ii) is capable of hybridizing under conditions as recited in claim 102 to the complement of SEQ ID NO: 1.

As set forth previously, the specification discloses TGF-β binding-proteins (BEER, SOST protein or sclerostin) that are capable to bind to BMP and prevent its binding to the receptors, and therefore, exhibit BMP antagonistic activity and decrease bone mineral content *in vivo*. The specification discloses a human BEER (SEQ ID NO: 1) and two variants of human BEER (V10I of SEQ ID NO: 5 and P38R of SEQ ID NO: 7), a vervet BEER (SEQ ID NO: 9), a mouse BEER (SEQ ID NO: 11), a rat BEER (SEQ ID NO: 13), and a bovine BEER (SEQ ID NO: 15). The specification discloses that these sclerostin proteins retain a cysteine backbone comprising eight cysteines (Fig. 1). However, the guidance provided in the specification, i.e., retention of the cysteine

backbone, and knowledge of conserved regions in other mammalian species and human variants, is not sufficient for the encompassed genus. First, without extensive structural and functional analysis, one of ordinary skill in the art would not know if the variants identified by the recited hybridization screening would retain such a structure: i.e., retention of the cysteine backbone, and would retain the activity: i.e., decreasing bone mineral content. While making mutants to a given protein (e.g., substitutions at certain positions) by mutagenesis based upon the guidance of the structural feature is routine, however, analyzing and determining a large number of variants generated by a screening method for a particular structural and functional characteristics requires an extremely large quantity of experimentation, which is undue. Second, the recited hybridization, i.e., hybridization at 45°C, followed by two washes at 45-50°C, allows a high degree of sequence variation, as discussed in the previous office action. Applicant asserts that under the wash conditions recited in claim 88, it would be estimated that about 80% homology is required for successful hybridization. However, it is unclear from Applicant's responses filed 27 May 2008 and 21 August 2007 where the 80% homology is come from. Applicant only provides a general formula for calculating Tm without identifying each parameter, and no calculation is provided. Caccone et al. (J. Mol. Evol., 1988, 27(3):212-216) teaches that a delta Tm of 1 degree C corresponds to 1.7% base pair mismatch (see Abstract). Even the hybridization condition yields variants having about 80% homology, which is, however, still beyond the scope encompassed by the sclerostin proteins Applicant has disclosed (SEQ ID NOs: 1, 5, 7, 9, 11, 13 and 15). The scope of patent protection sought by Applicant as defined by the

claim fails to correlate reasonably with the scope of enabling disclosure set forth in the specification. Third, the art teaches that certain positions in a sequence are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites, and these regions can tolerate only relatively conservative substitutions or no substitutions. For example, Groppe et al. (Nature, 2002, 42:636-642) made a number of single-amino acid mutants of Noggin, another BMP antagonist having the cysteine knot structure. Groppe et al. teach that although the folding and stability of these mutants is undisturbed, and the cysteine knot structure is retained, these mutants exhibit varying BMP-7 binding affinity, from unperturbed, to diminished, to abolished (pp. 638-pp. 639, section “Binding affinity of Noggin variants in vitro”). Further, Ellies et al. (J. Bone Miner. Res., 2006, 21(11):1738-1749) studied the functional interaction between SOST or Wise and LRP5/LRP6 in regulating bone deposition. Ellies et al. teach that replacing three residues (GGR to AVS) of SOST (the variant retains the cysteine knot structure) reduces binding to LRP6 (pp. 1747, Fig. 7). Therefore, the state of art teaches that it is unpredictable the effects of amino acid residue changes of a cysteine knot-protein on its function/activity. The specification does not provided support that retention of the cysteine backbone is sufficient to render the polypeptide the functional characteristics.

With regard to claims 101 and 103-106, there is no recitation of “naturally occurring polynucleotides”. Instead, the claims read on an antibody or an antibody

fragment thereof that binds to a fragment of the polypeptide encoded by SEQ ID NO: 1 (the claim language "a polypeptide encoded by SEQ ID No: 1" reads on a fragment).

With regard to claim 102, the same reasoning as set forth above applies to the variants of SEQ ID NO: 1.

With regard to make antibodies comprising effector or reporter molecules, the specification on pages 38-40 describes conjugating the antibody to molecules, such as antineoplastic agents, bacterial or plant toxins, enzymes, polymers, radionuclides, chelated metals. The specification however, does not teach, for example, how to make and use an anti-TGF-β binding protein antibody comprising any nucleic acid?

Based on the reasons set forth above and previously, the specification dose not satisfy the requirement of enablement because the amount of experimentation required is undue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 101 and 103-106 remain rejected under 35 U.S.C. 102(e) as being anticipated by Queen et al. (U. S. Patent No: 6,180,370 B1, which has a priority filing on 28 December 1988), for reasons set forth in the previous office action.

Applicant argues that the amendment to claim 101 has overcome the rejection.

Applicant's argument has been fully considered, but has been found to be partially persuasive.

Claim 101 now recites "wherein the polypeptide binds to a polypeptide encoded by SEQ ID NO: 1". The phrase "a polypeptide encoded by SEQ ID NO: 1" still reads on fragments or portions of SEQ ID NO: 1. The '370 patent teaches humanized immunoglobulins and antigen-biding fragments thereof, e.g., Fab, Fv, and $(Fab')_2$, that have an affinity of K_a greater than 10^7 M^{-1} (col. 58, table 6; col. 11, lines 21-37). The '370 patent teaches that the antibodies may be labeled, e.g., with enzymes, radionucleotides, and fluors (col. 20, lines 21-31). Since the claims encompasses an antibody, or an antibody fragment thereof, that binds to a fragment or a portion encoded by SEQ ID NO: 1, the antibodies taught in the '370 patent meet the limitation of the instant antibodies. Amending the claim to recite "the polypeptide encoded by SEQ ID NO: 1" would obviate the rejection.

Double Patenting

Claims 88, 89 and 91-100 remain rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-8 of U. S. Patent No: 6,803,453 for reasons set forth in the previous office actions.

Applicant has requested that the rejection be held in abeyance until there is an indication of allowable subject mater, and at that time, Applicant will consider filing a terminal disclaimer.

Conclusion

CLAIM 89 IS ALLOWABLE.

CLAIMS 88, 91-96 AND 101-106 ARE REJECTED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
July 23, 2008

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646